UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/740,256	12/18/2003	James E. Dahlberg	FORS-08497	1902

7590 12/19/2005

Mary Ann D. Brow
MEDLEN & CARROLL, LLP
Suite 350
101 Howard Street
San Francisco, CA 94105

EXAMINER	
BABIC, CHRISTOPHER M	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 12/19/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/740,256	DAHLBERG ET AL.	
	Examiner	Art Unit	
	Christopher M. Babic	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 September 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32-56* is/are pending in the application.

4a) Of the above claim(s) *35,37 and 38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-34,36, and 39-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12/18/2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 1/6/05
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Sequence Compliance Notice*.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Let-7 miRNA (Claim 54), readable on Claims 33-56, and, the polymerase chain reaction (PCR), drawn to Claim 36 and 44 in the reply filed on September 15, 2005 is acknowledged. Claims 35, 37, and 38 are hereby withdrawn as being drawn to a non-elected detection assay.

Sequence Rules Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825) before the application can be examined under 35 U.S.C. §§ 131 and 132.

Applicant is given time of reply to this office action within which to comply with the sequence rules, 37 C.F.R. §§ 1.821-1.825. Failure to comply with these requirements will result in **abandonment** of the application under 37 C.F.R. § 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 C.F.R. § 1.136. In no case may an applicant extend the

period for response beyond the six month statutory period. Direct the response to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the response.

Figures 12, 26, and 27 contain sequences without SEQ ID NOs. If these sequences are included in the sequence listing provide by Applicant, the specification should be amended to include the SEQ ID NOs. If these sequences were not included in the sequence listing filed August 30, 2002. Applicant should provide a substitute sequence listing and a CRF that include those sequences.

Specification

Applicant is reminded of the proper content of an abstract of the disclosure.

A patent abstract is a concise statement of the technical disclosure of the patent and should include that which is new in the art to which the invention pertains. If the patent is of a basic nature, the entire technical disclosure may be new in the art, and the abstract should be directed to the entire disclosure. If the patent is in the nature of an improvement in an old apparatus, process, product, or composition, the abstract should include the technical disclosure of the improvement. In certain patents, particularly those for compounds and compositions, wherein the process for making and/or the use thereof are not obvious, the abstract should set forth a process for making and/or use thereof. If the new technical disclosure involves modifications or alternatives, the abstract should mention by way of example the preferred modification or alternative.

The abstract should not refer to purported merits or speculative applications of the invention and should not compare the invention with the prior art.

Where applicable, the abstract should include the following:

(1) if a machine or apparatus, its organization and operation;
(2) if an article, its method of making;
(3) if a chemical compound, its identity and use;
(4) if a mixture, its ingredients;
(5) if a process, the steps.

Extensive mechanical and design details of apparatus should not be given.

The abstract of the disclosure is objected to because the word "improved" is considered to impart purported merits. Correction is required. See MPEP § 608.01(b).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. Claim 32 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 32, and all claims dependent thereof, are indefinite because the phrase "...wherein said second region *can* form a hairpin loop when said probe is hybridized..." renders the claim language unclear as to whether the limitation(s) set forth are part of the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

1. Claims 32, 33, 48-52, and 54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bagwell et al. (U.S. 5,607,834) in view of Lau et al. ("An Abundant Class of Tiny RNAs with Probable Regulatory Roles in *Caenorhabditis elegans*. Science. 26 October 2001. Vol. 294: Pages 858-862).

With regard to Claim 32, Bagwell et al. disclose a method for analyzing RNA (Figures 1; Column 3, Lines 45-67, for example) comprising: a) contacting RNA with a probe to form an RNA detection structure (Figures 1; Column 3, Lines 50-55, for example), wherein said probe comprises a first region that is complementary to said RNA and a second region that is not complementary to said RNA (Figures 1-6; Column 3, Lines 5-45, for example), wherein said second region can form a hairpin loop when said probe is hybridized to said RNA (Figures 1-6; Column 3, Lines 5-45, for example); and b) detecting said RNA detection structure (Column 3, Lines 55-60; Column 8,9, for example). Bagwell et al. do not specifically disclose microRNA detection.

Lau et al. disclose two types of short RNAs, both about 21 to 25 nucleotides (21-25 nt) in length (lin-4 and let-7) (i.e. microRNA (miRNA)) (Abstract; Table 1, for example).

Based on the combined disclosures of the applied references, one of ordinary skill in the art at the time of invention would have had a reasonable expectation of success practicing the RNA detection methods disclosed by Bagwell et al. further comprising the detection of microRNA, an obvious structurally equivalent species of the molecule RNA. At the time of invention, the disclosure of Lau et al. clearly would have

provided the instruction necessary for one of ordinary skill in the art to practice the methods as claimed. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of invention to practice the instant methods as claimed.

With regard to Claims 33 and 48, Bagwell et al. disclose nucleic acid detection and quantitation (Column 4, Lines 50-55; Columns 8,9, for example).

With regard to Claims 49, Bagwell et al. disclose identification of unique sequences in total RNA (Column 1, Lines 20-40, for example).

With regard to Claims 50, Bagwell et al. disclose RNA extraction from tissue culture (Column 1, Lines 20-40, for example).

With regard to Claim 51 and 52, Lau et al. disclose a plurality of different miRNAs 21-22 nucleotides in length (Page 860, Table 1, for example).

With regard to Claim 54, Lau et al. disclose Let-7 miRNA (Abstract; Table 1, for example).

2. Claims 32, 33, 36, and 39-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nazarenko et al. (U.S. 5,866,336) in view of Lau et al. ("An Abundant Class of Tiny RNAs with Probable Regulatory Roles in *Caenorhabditis elegans*. Science. 26 October 2001. Vol. 294: Pages 858-862).

With regard to Claim 32, Nazarenko et al. disclose a method for analyzing RNA (Figures 1,2; Column 23, Examples 5.2,5.2.1, for example) comprising: a) contacting RNA with a probe to form an RNA detection structure (Figures 1,2; Column 23,

Examples 5.2,5.2.1, for example), wherein said probe comprises a first region that is complementary to said RNA and a second region that is not complementary to said RNA (Figures 1,2; Column19, Example 5.1.1, for example), wherein said second region can form a hairpin loop when said probe is hybridized to said RNA ((Figures 1,2; Column19, Example 5.1.1, for example); and b) detecting said RNA detection structure (Column 23, Examples 5.2,5.2.1, for example). Nazarenko et al. do not specifically disclose microRNA detection.

Lau et al. disclose two types of short RNAs, both about 21 to 25 nucleotides (21-25 nt) in length (lin-4 and let-7) (i.e. microRNA (miRNA)) (Abstract; Table 1, for example).

Based on the combined disclosures of the applied references, one of ordinary skill in the art at the time of invention would have had a reasonable expectation of success practicing the RNA detection methods disclosed by Nazarenko et al. further comprising the detection of microRNA, an obvious structurally equivalent species of the molecule RNA. At the time of invention, the disclosure of Lau et al. clearly would have provided the instruction necessary for one of ordinary skill in the art to practice the methods as claimed. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of invention to practice the instant methods as claimed.

With regard to Claims 33 and 48, Nazarenko et al. disclose nucleic acid detection and quantitation (Figure 21, for example).

With regard to Claims 36 and 47, Nazarenko et al. disclose use of a detection assay that employs polymerase chain reaction (PCR) (Column 23, Examples 5.2,5.2.1, for example).

With regard to Claims 39-41, Nazarenko et al. disclose labeled probe configures for FRET detection (Figures 1,2; Column 19, Example 5.1.1, for example).

With regard to Claims 42 and 43, Nazarenko et al. disclose a labeled probe having a first conformation when not hybridized in a duplex and a second conformation when hybridized in a duplex thereby increasing fluorescence when hybridized in a duplex (Figures 1,2; Column 23, Examples 5.2,5.2.1, for example).

With regard to Claims 44-46, Nazarenko et al. disclose the TaqMan assay (Column 5, Lines 30-45). It is noted that the TaqMan assay was a well known nucleic acid detection assay at the time of invention as demonstrated by the disclosure of Nazarenko et al. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of invention to practice the instant methods as claimed.

With regard to Claim 49, Nazarenko et al. disclose identification of unique sequences in total RNA (Column 31, Lines 5-15, for example).

With regard to Claim 50, Nazarenko et al. disclose a cell lysate (Column 38, Lines 25-35, for example).

With regard to Claim 51 and 52, Lau et al. disclose a plurality of different miRNAs 21-22 nucleotides in length (Page 860, Table 1, for example). Furthermore, Nazarenko et al. disclose multiplex detection methods (Column 31, Lines 5-15, for example).

With regard to Claim 53, Nazarenko et al. disclose allele-specific PCR (ASP) (Column 25, Example 5.2.1.1, for example).

With regard to Claim 54, Lau et al. disclose Let-7 miRNA (Abstract; Table 1, for example).

With regard to Claim 55, Nazarenko et al. disclose nucleotide analogs (Column 16, Lines 5-45, for example).

3. Claim 34 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bagwell et al. (U.S. 5,607,834) in view of Lau et al. ("An Abundant Class of Tiny RNAs with Probable Regulatory Roles in *Caenorhabditis elegans*. Science. 26 October 2001. Vol. 294: Pages 858-862), in further view of Prudent et al. (U.S. 5,985,557).

The methods of Bagwell et al. have been outlined in above rejections. Bagwell et al. does not specifically disclose forming an invasive cleavage structure, cleaving said invasive cleavage structure, and detecting the cleavage of said invasive cleavage structure.

Prudent et al. disclose forming an invasive cleavage structure (Figures 16A-E, Figure 29, for example), cleaving said invasive cleavage structure (Columns 31-39, Example III, for example), and detecting the cleavage of said invasive cleavage structure(Columns 31-39, Example III, for example). They further disclose that the invader-directed or "invasive" cleavage assay is useful in the detection and

quantification of individual variants or alleles in a mixed sample population (Column 38, Lines 15-60).

Based on the combined disclosures of the applied references, one of ordinary skill in the art at the time of invention would have had a reasonable expectation of success practicing the nucleic acid detection method of Bagwell et al. further comprising detection using an invasive cleavage assay. The motivation to do so, provided by Prudent et al., would have been to detect and quantify individual variants or alleles in a mixed sample population. At the time of invention, the disclosure of Prudent et al. clearly would have provided the instruction necessary for one of ordinary skill in the art to practice the methods as claimed. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of invention to practice the instant methods as claimed.

4. Claim 34 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nazarenko et al. (U.S. 5,866,336) in view of Lau et al. ("An Abundant Class of Tiny RNAs with Probable Regulatory Roles in *Caenorhabditis elegans*. Science. 26 October 2001. Vol. 294: Pages 858-862), in further view of Prudent et al. (U.S. 5,985,557).

The methods of Nazarenko et al. have been outlined in above rejections. Bagwell et al. does not specifically disclose forming an invasive cleavage structure, cleaving said invasive cleavage structure, and detecting the cleavage of said invasive cleavage structure.

Prudent et al. disclose forming an invasive cleavage structure (Figures 16A-E, Figure 29, for example), cleaving said invasive cleavage structure (Columns 31-39, Example III, for example), and detecting the cleavage of said invasive cleavage structure(Columns 31-39, Example III, for example). They further disclose that the invader-directed or "invasive" cleavage assay is useful in the detection and quantification of individual variants or alleles in a mixed sample population (Column 38, Lines 15-60).

Based on the combined disclosures of the applied references, one of ordinary skill in the art at the time of invention would have had a reasonable expectation of success practicing the nucleic acid detection method of Nazarenko et al. further comprising detection using an invasive cleavage assay. The motivation to do so, provided by Prudent et al., would have been to detect and quantify individual variants or alleles in a mixed sample population. At the time of invention, the disclosure of Prudent et al. clearly would have provided the instruction necessary for one of ordinary skill in the art to practice the methods as claimed. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of invention to practice the instant methods as claimed.

5. Claim 56 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bagwell et al. (U.S. 5,607,834) in view of Lau et al. ("An Abundant Class of Tiny RNAs with Probable Regulatory Roles in *Caenorhabditis elegans*. Science. 26

October 2001. Vol. 294: Pages 858-862), in further view of Hyldig-Nielsin et al. (U.S. 5,985,563).

The methods of Bagwell et al. have been outlined in above rejections. Bagwell et al. does not specifically disclose the use of peptide nucleic acids (PNAs).

Hyldig-Nielsin et al. disclose an assay using PNA probes (Column 17, Lines 30-45; Columns 19,20, Example 1, for example). They further disclose that PNAs have a higher thermal instability of mismatching bases whereby PNAs exhibit a greater specificity for their complementary nucleic acids than traditionally used nucleic acid probes (Column 2, Lines 40-55).

Based on the combined disclosures of the applied references, one of ordinary skill in the art at the time of invention would have had a reasonable expectation of success practicing the nucleic acid detection method of Bagwell et al. further comprising detection using PNA probes. The motivation to do so, provided by Hyldig-Nielsin et al., would have been the fact that PNAs exhibit a greater specificity for their complementary nucleic acids than traditionally used nucleic acid probes. At the time of invention, the disclosure of Hyldig-Nielsin et al. clearly would have provided the instruction necessary for one of ordinary skill in the art to practice the methods as claimed. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of invention to practice the instant methods as claimed.

6. Claim 56 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nazarenko et al. (U.S. 5,866,336) in view of Lau et al. ("An Abundant Class of Tiny RNAs with Probable Regulatory Roles in *Caenorhabditis elegans*. Science. 26 October 2001. Vol. 294: Pages 858-862), in further view of Hyldig-Nielsin et al. (U.S. 5,985,563).

The methods of Nazarenko et al. have been outlined in above rejections. Nazarenko et al. does not specifically disclose the use of peptide nucleic acids (PNAs).

Hyldig-Nielsin et al. disclose an assay using PNA probes (Column 17, Lines 30-45; Columns 19,20, Example 1, for example). They further disclose that PNAs have a higher thermal instability of mismatching bases whereby PNAs exhibit a greater specificity for their complementary nucleic acids than traditionally used nucleic acid probes (Column 2, Lines 40-55).

Based on the combined disclosures of the applied references, one of ordinary skill in the art at the time of invention would have had a reasonable expectation of success practicing the nucleic acid detection method of Nazarenko et al. further comprising detection using PNA probes. The motivation to do so, provided by Hyldig-Nielsin et al., would have been the fact that PNAs exhibit a greater specificity for their complementary nucleic acids than traditionally used nucleic acid probes. At the time of invention, the disclosure of Hyldig-Nielsin et al. clearly would have provided the instruction necessary for one of ordinary skill in the art to practice the methods as

claimed. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of invention to practice the instant methods as claimed.

Conclusion

No claims are allowed. No claims are free of the prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher M. Babic whose telephone number is 571-272-8507. The examiner can normally be reached on Monday-Friday 7:00AM to 4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

12/12/05

GARY BENZION, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Notice to Comply	Application No.	Applicant(s)
	10/740256	Dahlberg et al.
	Examiner	Art Unit
	Christopher M. Babic	1637

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1; 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒ 7. Other: See Office Action

Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
For CRF Submission Help, call (703) 308-4212
PatentIn Software Program Support
Technical Assistance.....703-287-0200
To Purchase PatentIn Software.....703-306-2600

PLEASE RETURN A COPY OF THIS NOTICE WITH YOUR REPLY